Editorials

Future Trends in the Incidence and Management of Prostate Cancer

THE MANAGEMENT OF prostatic diseases has received considerable attention in both the scientific and lay press over the past five years. Once the domain of urologists, prostatic hyperplasia and carcinoma have now become diseases of interest to primary care physicians, oncologists, endocrinologists, epidemiologists, public health officials, talk show hosts, and television anchorpersons. Histologic evidence of benign hyperplasia is nearly ubiquitous among America's elderly men, with roughly 40 million men at risk for voiding dysfunction and morbidity from the disease. Histologic evidence of prostatic carcinoma is frighteningly common, with about 30% of all men older than 60 showing carcinoma, as reported in several autopsy series. A recent autopsy study of young trauma victims (aged 39 years or younger) revealed that 33% of men in the 30- to 39-year age group had microscopic evidence of prostatic carcinoma on careful examination of the gland. Whether "clinically significant" prostate cancer would have developed in these men in their lifetime is unknown; nevertheless, the study findings underscored both the high prevalence of histologically detectable prostate cancer and the often latent nature of this unusual malignant disorder. Although the prevalence of prostatic carcinoma is difficult to define, more than 25 million men are estimated to have occult prostatic carcinoma. With staggering numbers such as these, it is easy to understand why interest in prostatic diseases has spread to nonurologists.

The medical and economic effects of prostatic diseases promise to become even more serious in the next 20 years, as the men born in the post-World War II era (the "baby-boomers") reach the age when prostatic disease becomes manifest. The treatment of prostatic hyperplasia and carcinoma already consumes a substantial percentage of the Medicare and general health care budget—with estimates of as high as $1 billion spent annually in direct and indirect costs. At the present rate of rise in the incidence of clinically significant prostatic carcinoma (macroscopic or biochemically detectable cancer), by the year 2000 more than 200,000 cases will be diagnosed each year in the United States. The overwhelming majority of men with this diagnosis are vigorous and healthy and would warrant either curative (radical surgery or irradiation) or palliative therapy. At a conservative cost estimate of $10,000 to $20,000 per case diagnosed for either curative therapy or lifetime palliative care, the annual cost for prostate cancer alone could soon approach $2 billion to $4 billion. In an era of medical fiscal constraints, these increases would be unacceptably burdensome.

The well-written treatise on hormonal therapy for metastatic prostate cancer by Marko Gudziak, MD, and Anthony Smith, MD, elsewhere in this issue of the journal covers the rationale for hormonal ablation of systemic prostate cancer in complete detail.[1] Among the most important elements of this work is the cost analysis contained in their Table 3. Orchiectomy is the most cost-effective means of managing disseminated prostate cancer. Unfortunately, when given a choice between surgical (orchiectomy) and medical (luteinizing hormone-releasing hormone [LH-RH] analogue) castration, most men (roughly 80%) choose the more expensive option—medical hormonal ablation. In the present social climate, it is unlikely that men will be denied their choice of medical therapy with an LH-RH analogue (leuprolide or goserelin). Thus, a minimum cost of $10,000 can be expected for treating a case of metastatic prostate cancer over the patient's lifetime.

A growing wealth of evidence also supports the use of the antiandrogen flutamide (Eulexin) in an effort to neutralize androgens of adrenal origin, which have been shown to stimulate prostate cancer growth. In most trials, adding an antiandrogen has meant a survival advantage of 6 to 19 months for most men taking the drug, along with some form of castration. Patients with poor prognostic indicators and a poor performance status do not benefit from combined androgen blockade, so antiandrogen therapy should not be used in these men. This group is a minority, so cost savings from this approach would be minimal. Thus, an additional $5,000 expense can be expected from treating incurable cancer. When coupled with the cost of castration, the treatment of disseminated prostate cancer approaches $8,000 to $15,000 per case. These figures exclude the costs of diagnosing and monitoring the disease and of treating patients in their final 6 to 12 months of life when the cancer develops resistance to hormonal deprivation.

Clearly, treating prostate cancer in its most advanced stages is an expensive proposition. The cost of potentially curative therapy is likewise appreciable. The cost of radiation therapy and radical prostatectomy varies regionally, but is in the range of $10,000 to $15,000. Naturally, for some men localized therapy will fail, and they will require treatment of systemic disease; others may suffer complications from radiation or surgical therapy with their attendant costs. Although a novel, minimally invasive approach to local treatment—cryosurgical ablation of the prostate—offers the possibility of an effective treatment of localized disease in, possibly, an outpatient setting, greater experience will be needed with this technique before it can be considered effective in curing or controlling cancer. The cost of cryotherapy could be less than that of radical surgery—with the obligate four- to seven-day inpatient stay for a major operation, and also less expensive than 70 Gy of external irradiation. Even with more efficiently delivered care of localized prostate cancer, the cost of treating prostatic cancer with present methods is substantial.

Current research into prostate cancer treatment includes outcome analysis whereby the efficacy, morbidity, and cost of competing modalities are compared. Because

of the indolent nature of many cases of prostate cancer, the benefits and risks of deferred treatment—or even no treatment at all—must be compared with those of aggressive management. In this country, we are already seeing the benefits of public education about healthier lifestyles. Dietary modification, smoking cessation, daily exercise, safer homes and highways, and better medical care—especially cardiac and hypertensive care—will all contribute to a greater longevity for American men. Although prostate cancer will not present a mortal threat to every man who is diagnosed with the disease, morbidity from localized and disseminated disease is considerable and costly. As American men live longer, the potential for morbidity from localized tumor progression or advancing systemic disease will increase, and the expense of treating more advanced disease will be substantial. Although active observation of patients with prostate cancer with deferred treatment has its proponents, this may end up being an expensive experiment as men in excellent general health require many treatments to palliate for advancing cancer. Our hope is that carefully designed prospective studies incorporating outcomes research tools will soon yield solutions to these vexing issues.

In the basic and clinical research areas, however, rests the future of prostate cancer management. A nationwide prostate cancer prevention trial is currently accruing men in a seven-year experiment to determine whether the drug finasteride (Proscar), an inhibitor of the potent androgen, dihydrotestosterone, is effective in preventing prostate cancer development. This randomized, prospective, placebo-controlled and double-blind trial has sparked considerable controversy because the chemopreventive abilities of finasteride are still to be proved. But it offers some hope of stemming the tide of the onrushing prostate cancer "epidemic."

Epidemiologic studies have recently linked dietary fat and cholesterol intake to prostate cancer occurrence. With changes in American dietary habits, the incidence of prostate cancer may stabilize as Americans consume less dietary fat. In a related finding, levels of vitamin D, both from dietary intake and from ultraviolet sources, may promote prostatic carcinogenesis. Lifestyle changes eliminating either of these risks may lower the prostate cancer risk.

Finally, genetic-linkage analysis techniques are being used in cases of familial prostate cancer in hopes of identifying regions of the genome responsible for the initiation or promotion of prostate cancer. If genetically engineered tumor suppressor regions can be inserted into the host genome, prostatic carcinogenesis can be interrupted in its earliest stages—if not prevented altogether. Although these research efforts are expensive, the possible future benefits must be considered in light of the increasing incidence of prostate cancer, increasing costs of treating the disease, and shrinking health care funds available. Although current treatment modalities may be satisfying to those who treat prostate cancer patients, we must recognize that these methods will become increasingly costly at a time when costs must decline. In innovative basic science laboratories around the country, research in breakthrough technologies offers the only hope for gaining control of this disease.

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Moles and Melanoma—New Method in the Madness

SINCE THE INITIAL histologic recognition of melanocytic nevi ("moles") and cutaneous malignant melanoma, a poorly understood relationship between these two disorders has persisted to this day.[1-3] Although melanocytic neoplasia is the focus of increasing research, fundamental knowledge concerning it remains limited but has nonetheless provoked considerable controversy and debate. Both nevi and melanoma seem to be inextricably linked because of the common clinical history of an antecedent nevus at the site of melanoma (reports vary from 19% to 85%), the histologic contiguity of nevi with melanoma (estimates range from 18% to 72%), and the observation that melanoma patients often have numerous, unusual, or "funny" nevi.[1] Because of the rapidly increasing incidence of cutaneous malignant melanoma among white populations worldwide in recent years and the recognition that melanocytic nevi (both typical and atypical) are in fact important risk factors for cutaneous melanoma, there are compelling reasons to better understand this curious relationship.

Given the importance of the relationship between nevi and melanoma, it is surprising how little has been known until recently about melanocytic nevi. What are the origin and nature of these peculiar growths? It seems clear that nevi originate from cells migrating from the neural crest to the skin.[1-3] The immediate origin of nevi seems to be the proliferation of intraepidermal melanocytes, the subsequent migration into the dermis, and terminal differentiation. An alternative hypothesis is that these migratory cells from the neural crest may reach the dermis as nerve sheath-associated cells, with the epidermis as the final destination and place of terminal differentiation.[4] Irrespective of the sequence of nevus development, little is known concerning the mechanisms of proliferation, cell migration, and differentiation in nevi.

Because melanocytic nevi are not considered normal structures, there has been a long-standing debate as to whether they are hamartomatous or neoplastic.[2,3] Nevi present at birth—congenital nevi, particularly giant varieties—probably are hamartomatous. On the other hand, there is also mounting evidence from experiments that melanocytic nevi in general are indeed neoplastic and are lesions intermediate in the tumor progression of melanocytes to melanoma.[5-12] The cells that make up nevi have been called "nevus cells" historically. These cells differ from basilar intraepidermal melanocytes because of their